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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,046	11/20/2001	Frederic J. de Sauvage	P1405R1C1	1433

9157 7590 03/02/2009

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
03/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,046	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 11/17/08 has been entered.

Status of Application, Amendments and/or Claims

On 11/17/08, Applicants filed an Amendment After Final. As noted above, this amendment has been entered in view of the Request for Continued Examination (RCE) (filed on 1/12/09). The 11/17/08 amendment does not include any claim amendments (each pending claim listed as "Previously Presented").

Claims 29, 30, 36-40, 46-49 and 52-54 are pending in the application.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al (18 February 1998. Nat Genet. 18(2): 104-6) in view of Tso et al (U.S. Patent No. 5,932,448, published 8/3/88, and filed 11/29/1991). This rejection was set forth previously and maintained at pg 3-7 of the 7/15/08 Office Action.

Claims 29, 30, 39, 40 and 49 each encompass a monoclonal antibody that "specifically binds" to a patched-2 polypeptide of instant SEQ ID NO: 2, or variants of SEQ ID NO: 2 that are at least 95% identical and bind to a *hedgehog* or *Smoothened* polypeptide. The remaining claims depend from claims 29, 39 or 49 and limit the antibodies to those that are humanized (claims 36, 46 and 52), bispecific (claims 37, 47 and 53), or heteroconjugated (claims 38, 48 and 54).

Motoyama et al teach the mouse gene Ptch2 that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID NO: 2 (which is the human patched-2 polypeptide). See the alignment included below. Motoyama et al further teach that the mouse gene Ptch2 is expressed in the adult eye and in the epithelial cells of the developing hair, tooth and whisker (pg 105). Motoyama does not teach an antibody to the mouse patched-2 polypeptide.

Tso teaches general methods for producing bispecific antibodies (col 1, line 62-67); including the use of monoclonal antibodies in production of bispecific antibodies (col 7, line 19); humanized monoclonal antibodies for use in bispecific antibodies (col 2, lines 46-47); and chemical cross-linking of two antibodies to produce a bispecific antibody (col 1, lines 34-35). Tso et al further teach that the antibodies have general uses applicable for use with any polypeptide, such as cross-linking a detection agent for purposes of detection; i.e., the bi-specific antibody binds both the target molecule to be detected and a detection agent such as horseradish peroxidase (see col 11, lines 52-55). The instant specification defines heteroconjugated antibodies as “antibodies composed of two covalently joined antibodies (pg 26). Thus, the bispecific antibody taught by Tso meets the definition of a “heteroconjugated” antibody as defined by the specification.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make bispecific antibodies as taught by Tso to the mouse patched-2 polypeptide taught by Motoyama et al. The person of ordinary skill in the art would have been motivated to do so in order to detect the expression of the mouse patched-2 polypeptide in mouse tissues and in particular to determine if the polypeptide expression is the same as the gene expression taught by Motoyama et al. The person

of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse patched-2 polypeptide, and Tso teaches general methods necessary to produce bispecific antibodies to any polypeptide sequence and that said antibodies can be used for detection purposes.

Such antibodies are encompassed by the instant claims for the following reasons. The pool of antibodies generated against the mouse patched-2 polypeptide taught by Motoyama et al would inherently include antibodies that also bind to instant SEQ ID NO: 2 (human patched-2 polypeptide). The relevant art provides evidence that "the size of an epitope is approximately equivalent to 5-7 amino acids" (see pg 40 of Benjamini et al, 1991. Immunology: A Short Course, 2nd edition; cited here solely to support inherency). An alignment between the mouse patched-2 polypeptide taught by Motoyama et al and instant SEQ ID NO: 2 reveals numerous regions of 100% identity that comprise 5 or more amino acids (see alignment in the next paragraph below). These regions of exact identity therefore contain identical epitopes that would generate antibodies that would bind to either polypeptide. The term “specifically binds” is not defined in the specification as excluding antibodies that bind to the same epitope in other polypeptides (e.g., mouse patched-2); and therefore broadly encompasses antibodies that bind to the same epitope in two different sequences. Therefore, the set of antibodies generated against the mouse patched-2 polypeptide taught by Motoyama et al would inherently include antibodies that specifically bind to an epitope also found within the human polypeptide of SEQ ID NO: 2.

An alignment of instant SEQ ID NO: 2 ("Qy") and the mouse patched-2 polypeptide taught by Motoyama et al ("Db") is shown here:

```
Query Match             89.3%;  Score 5599;  DB 2;  Length 1182;
  Best Local Similarity   90.9%;  Pred. No. 0;
  Matches 1074;  Conservative   43;  Mismatches   64;  Indels    0;  Gaps    0;

Qy          1 MTRSPPLRELPPSYTPPARTAAPQILAGSLKAPLWLRAYFQGLLFSLGCGIQRHCGKVLF 60
              | |   | ||||||||||:::|| |||||:|||||||||||||||| ||:|||||||
Db          1 MVRPLSLGELPPSYTPPARSSAPHILAGSLQAPLWLRAYFQGLLFSLGCRIQKHCGKVLF 60

Qy         61 LGLLAFGALALGLRMAIIETNLEQLWVEVGSRVSQELHYTKEKLGEEAAYTSQMLIQTAR 120
              |||:||||||||||:|:|||:|||||||||||||||||||||||||||||||||||||||
Db         61 LGLVAFGALALGLRVAVIETDLEQLWVEVGSRVSQELHYTKEKLGEEAAYTSQMLIQTAH 120

Qy        121 QEGENILTPEALGLHLQAALTASKVQVSLYGKSWDLNKICYKSGVPLIENGMIEWMIEKL 180
              ||| |:|||||| |||||||||||||||||||||||||||||||||||||||||||| |||||
Db        121 QEGGNVLTPEALDLHLQAALTASKVQVSLYGKSWDLNKICYKSGVPLIENGMIERMIEKL 180

Qy        181 FPCVILTPLDCFWEGAKLQGGSAYLPGRPDIQWTNLDPEQLLEELGPFASLEGFRELLDK 240
              ||||||||||||||||||||||||||||||||||||||:||||||||||||||||||||||
Db        181 FPCVILTPLDCFWEGAKLQGGSAYLPGRPDIQWTNLDPQQLLEELGPFASLEGFRELLDK 240

Qy        241 AQVGQAYVGRPCLHPDDLHCPPSAPNHHSRQAPNVAHELSGGCHGFSHKFMHWQEELLLG 300
              |||||||||||||| ||| |||||||| ||||||||| |||||||||||||||||||||||
Db        241 AQVGQAYVGRPCLDPDDPHCPPSAPNRHSRQAPNVAQELSGGCHGFSHKFMHWQEELLLG 300
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Applicants' arguments (3/21/08; pg 4-7) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the 11/17/08 response, Applicants argue that "a sufficient motivation for one of ordinary skill in the art to make antibodies against the mouse patched-2 protein" has not been established. Applicants argue that that the cited motivation is applicable to any disclosed polypeptide, and not specific to the patched-2 polypeptide disclosed by Motoyama. Applicants argue that "neither reference teaches or suggests a specific motivation to create an antibody against the patched-2 protein". Applicants argue that there "is no teaching that such an antibody would have any specific or substantial utility to one of skill in the art except that it might be possible to create such an antibody to mouse patched-2" (pg 4-6). Applicants further argue that the skilled artisan must further

extrapolate that if such an antibody were created it would also necessarily have affinity for the human homologue.

Applicants' arguments have been fully considered but are not persuasive for the following reasons. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a sufficient motivation for the skilled artisan to make antibodies against the mouse patched-2 polypeptide taught by Motoyama et al has been set forth herein. As described above, the person of ordinary skill in the art would have been motivated to make an antibodies as taught by Tso et al to the mouse patched-2 polypeptide as taught by Motoyama et al in order to determine the detect the expression of the polypeptide in mouse tissues; in particular, to determine if the polypeptide expression is the same as the gene expression taught by Motoyama et al. This motivation is specific to the patched-2 polypeptide as taught by Motoyama et al. This motivation to combine the references does not come from either reference individually; rather, it is the combination of the teachings of the references that provides the motivation to create said antibodies. The skilled artisan does not need to "further extrapolate" that such an antibody would have affinity for the human homologue; as set forth above, such an antibody would inherently bind specifically to the human patched-2 polypeptide of SEQ ID NO: 2, absent evidence to the contrary (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). In other words, Applicants have not provided any evidence to indicate that the antibodies generated against the mouse patched-2 polypeptide taught by Motoyama et al would not bind the patched-2 polypeptide of SEQ ID NO: 2 of the instant application.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647